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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/388,899	09/02/1999	BEREND HOUWEN	10690/T/B/A	4619

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EXAMINER	
GABEL, GAILENE	
ART UNIT	PAPER NUMBER
1641	13

DATE MAILED: 04/22/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/388,899	Applicant(s) HOUWEN ET AL.	
	Examiner Gailene R. Gabel	Art Unit 1641	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 March 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-14* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-14* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 3/13/02 has been entered.

Amendment Entry

2. Applicant's preliminary amendment filed 3/7/02 in Paper No. 12 is acknowledged and has been entered. Claim 1 has been amended. Claims 12-14 have been added. Accordingly, claims 1-14 are pending and under examination.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

3. Claims 1-14 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1, step 1), part b) is indefinite in reciting, "at least one kind of neutrophilic cells" because it is unclear what kinds of neutrophilic types Applicant intends to encompass. Perhaps, Applicant intends to recite "at least one kind/type of (mature) granulocytic cell" encompassing neutrophils, eosinophils, and/or basophils.

Claim 1, step 3) is indefinite because it is unclear what Applicant intends to encompass in reciting, "a group of granulocytic cells". Specifically, it is unclear what "group" of the recited granulocytes, i.e. neutrophils, eosinophils, basophils, Applicant intends to "define". Alternatively, Applicant appears to intend to recite, "defining a group comprising granulocytes". Such recitation is consistent with Figure 2 of the specification and with newly recited claim 13.

Claim 1, step 4) is indefinite because it is unclear what Applicant intends to encompass in reciting, "distinguishing eosinophils and a group of neutrophilic cells in the defined group of granulocytic cells". Specifically, it is unclear what kinds/groups of neutrophilic cells Applicant intends to encompass and what "defined group" of the granulocytic cells Applicant intends to "distinguish". Perhaps, Applicant intends to recite, "distinguishing eosinophils from neutrophilic cells in the defined group comprising granulocytes". Such recitation is consistent with Figure 3 of the specification and with newly recited claim 12.

Claim 1, step 5), as amended, lacks antecedent support in reciting, "the defined group of the neutrophilic cells".

Claim 1, step 5) is indefinite because it is unclear what Applicant intends to encompass in reciting, "classifying the defined group of the neutrophilic cells into groups

of neutrophilic cells different in degree of maturity". Specifically, it is unclear what "defined group" of the recited neutrophilic cells Applicant intends to "classify". Perhaps, Applicant intends to recite, "classifying the neutrophilic cells into groups having different degrees of maturity". Such recitation is consistent with Figures 4-5 of the specification and with newly recited claim 14.

Same analogous comments and problems apply to claim 2.

Claim 12 is indefinite because it is unclear what Applicant intends to encompass in reciting, "the eosinophils and the group of neutrophilic cells are distinguished on the". Specifically, it is unclear what "group" of the recited neutrophilic cells Applicant intends to encompass. Perhaps, Applicant intends to recite, "the eosinophils are distinguished from the neutrophilic cells on the". Such recitation is consistent with Figure 3 of the specification and claim 1, step 4).

Claim 13 is indefinite because it is unclear what Applicant intends to encompass in reciting, "and the group granulocytic cells are distinguished". Specifically, it is unclear what "group" of the recited granulocytic cells Applicant intends to "distinguish". Perhaps, Applicant intends to recite, "and the group comprising granulocytic cells are distinguished". Such recitation is consistent with Figures 4-5 of the specification and with claim 1, step 3).

In claim 14, "according to the degree of maturity" should be "according to degrees of maturity" so as to be consistent with Figures 4-5 of the specification and claim 1, step 5).

Claim language set forth by Examiner is suggested but not required and offered only to assist Applicant in clearly defining the claimed invention.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless -
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

4. Claims 1-10 and 12-14 are rejected under 35 U.S.C. 102(b) as being anticipated by Bowen et al. (Laboratory Hematology, 1997).

Bowen et al. teach abnormal patterns of expression of CD16 and CD11b antigens by neutrophils in bone marrow of patients using flow cytometric monoclonal antibody-based, three color immunofluorescence technique which permits simultaneous characterization of different cell populations (see Abstract). In the study of Bowen et al., bone marrow was aspirated into blood collection tubes, stained using different monoclonal antibodies, then erythrocytes were lysed using Ortho Lyse. The monoclonal antibodies include anti-CD45 conjugated with Tri-Color, anti-CD16 conjugated with FITC, and anti-CD11b conjugated with PE. Five parameters which include SALS, FALS, Tri-color, FITC, and PE were measured using flow cytometry. In data analysis, Bowen teach that granulocytic cells can be defined on the basis of intensity of side scattered light (SALS) and fluorescence intensity by fluorescence

labeled leucocyte specific anti-CD45 antibodies wherein each gate can be set to include developing and mature granulocyte populations, i.e. neutrophils and eosinophils, and exclude agranular leucocyte populations (blasts, monocytes, and lymphocytes) which inherently have lower SALS (see page 294, column 1). Bowen also confirmed that peripheral blood neutrophil populations within varying maturation levels (promyelocytes, myelocytes, metamyelocytes, and band cells) are quantified within the CD11b and CD16 regions because both CD16 and CD 11b normally increase during the maturation of granulocytes from promyelocytic stage to segmented neutrophil stage (see page 294, column 2 and page 275, column 1). Bowen further observed that the manual percentage of band to segmented neutrophils correlated well with CD16 expression suggesting that in the course of granulocyte maturation, CD11b expression appears earlier and prior to the expression of CD16; therefore, anti-CD16 antibodies are more useful in defining granulocytes in later maturation stages than CD11b (see page 296, column 2). In conclusion, Bowen teach that simultaneous quantitation of SALS and fluorescent labeled monoclonal antibody binding to CD45, CD16, and CD11b define highly reproducible developmental maturation patterns of the granulocytic cell population series in flow cytometry.

5. Claims 1-10 and 12-14 are rejected under 35 U.S.C. 102(b) as being anticipated by Loken et al. (EP 0317516).

Loken et al. disclose a method and kit for classifying and counting lineages and stages of hematopoietic cells including leucocytes. Specifically, Loken et al. disclose

adding to a sample of bone marrow a first monoclonal antibody labeled with a first fluorochrome which specifically binds all leucocytes, in this case, anti-CD45 antibody. A second fluorochrome labeled monoclonal antibody specific to a subset of the leucocytes such as granulocytes is further added, in this case anti-CD16 and anti-CD11b are used for their ability to distinguish between granulocytic lineage, i.e. neutrophils and eosinophils, and myeloid maturation stages (see columns 2 and 6). Specifically, Loken et al. disclose assessment of myeloid maturation in bone marrow cells by staining with several monoclonal antibodies including anti-CD16, anti-CD11b, and anti-CD15 in combination with anti-CD45 (see column 9). Loken et al. teach that fluorochrome labels should be selected to have a similar excitation energy level but distinct emission spectra. In this case, Loken use FITC and PE which are conjugated directly or indirectly to antibodies in three-color flow cytometric analysis for measurement of their fluorescence intensity (see column 4). Loken et al. use flow cytometry to distinguish between cell lineages by cell size, granularity, and distribution of antibody binding to cells: FALS and SALS are used to separate cellular lineages based upon their optical and physical characteristics then SALS provides an approximation of cellular granularity which then provides a function of the presence (or absence) of structures such as nucleus and granules in the cells (see column 3 and 5). In conclusion, Loken disclose that by combining intensity of light scatter (FALS or SALS) and fluorescence intensity by different fluorochromes, various cell lineages and stages can be distinguished.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

6. Claim 11 is rejected under 35 U.S.C. 103(a) as being unpatentable over Bowen et al. (Laboratory Hematology, 1997) in view of McCarthy et al. (Journal of Immunological Methods, 1993).

Bowen et al. have been discussed supra. Bowen et al. fail to teach staining leucocytes after erythrocytes are removed from the hematological sample.

McCarthy et al. teach a flow cytometric procedure for the determination of surface antigens on leucocytes in whole blood including use of FITC labeled anti-CD16 and anti-CD11b antibodies. McCarthy et al. teach that Ficoll-Hypaque or dextran sedimentation are commonly used to purify and separate peripheral blood neutrophils

from other cells such as erythrocytes prior to labeling the neutrophils for flow cytometric analysis (see page 155, column 2).

It would have been obvious to one of ordinary skill in the art at the time of the instant invention to separate and purify leucocytes, such as neutrophils, from other cellular components such as erythrocytes using Ficoll-Hypaque and dextran sedimentation, as taught by McCarthy, prior to labeling of leucocytes in the cytometric analysis method of Bowen because McCarthy specifically taught that such procedures of cellular separation or removal from other cellular populations are conventional and well-known in the art so that an issue of when such a purification or separation procedure is introduced into a method of flow cytometric analysis, i.e. before or after binding of a label to desired cells, is an obvious design choice. There is no unexpected result in the order in which the leucocytes are stained prior to or subsequent to removal of the erythrocytes.

Remarks

6. Applicant's remarks filed 3/7/02 have been fully considered but they are not persuasive.

A) Applicant contends that the amendment of claim 1 and submission of new claims 12-14 are not anticipated by Bowen and Loken, and claim 11 is not suggested by the combination of Bowen or Loken with McCarthy.

In response, the disclosure of Bowen and Loken appear to read on the claims as currently recited. Specifically, claim 1 does not require that the eosinophils are

distinguished from other granulocytic populations or neutrophils using fluorescence intensity from the first fluorescence labeled antibody and fluorescence intensity from the second or third fluorescence labeled antibody in the 2D scattergram set forth in claim 12. Therefore, claims 1-10 and 12-14 are said to be anticipated by both Bowen and Loken. Further, claim 11 is said to be suggested by the combination of the teachings of both Bowen and Loken with McCarthy.

7. No claims are allowed.

8. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gailene R. Gabel whose telephone number is (703) 305-0807. The examiner can normally be reached on Monday to Thursday, 6:30 AM - 4:00 PM and alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Long Le can be reached on (703) 308-3399. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4242 for regular communications and (703) 308-4242 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

grg
April 21, 2002

Christopher L. Chin

CHRISTOPHER L. CHIN
PRIMARY EXAMINER
GROUP ~~1800~~ 1641